Access DB# 129279

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Truong, Duc Examiner # : 69332 Date: 8/6/04
Art Unit: 1711 Phone Number 302-687 Serial Number: 10/678,491
Mail Box and Bldg/Room Location: 6D71 Results Format Preferred (circle): [✓ PAPER] DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

SCIENTIFIC REFERENCE BR
Sci. & Tech. Info. Cntr
AUG 9
Pat. & T.M. Office

Title of Invention:

Inventors (please provide full names):

Earliest Priority Filing Date:

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issu appropriate serial number.*

Formula of claim 1. Thanks.

RELATED TO REQUEST #129241

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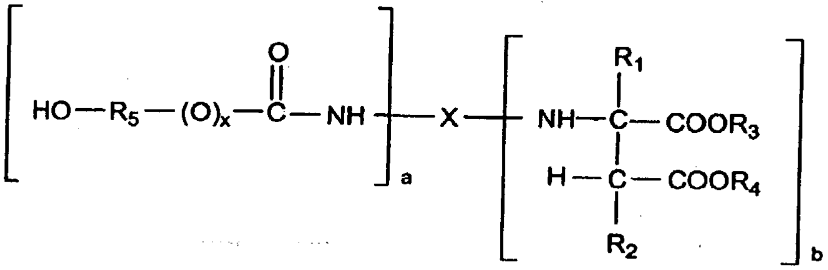
STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: EJ	NA Sequence (#)	STN
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed: 8-13-04	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (8-01)

WHAT IS CLAIMED IS:

1. An aspartate of the formula:



$$\left[HO-R_5-(O)_x-\overset{\overset{\displaystyle O}{\|}}{C}-NH \right]_a-X-\left[NH-\overset{\overset{\displaystyle R_1}{|}}{C}-COOR_3 \atop H-\underset{\underset{\displaystyle R_2}{|}}{C}-COOR_4 \right]_b$$

where

X represents an m-valent organic residue obtained by removing the primary amino group or groups from a mono or polyamine which has (cyclo)aliphatically bound amino groups and a number average molecular weight of 60 to 6000, and which may contain further functional groups that either are reactive with isocyanate groups or are inert to isocyanate groups at temperatures of up to 100°C,

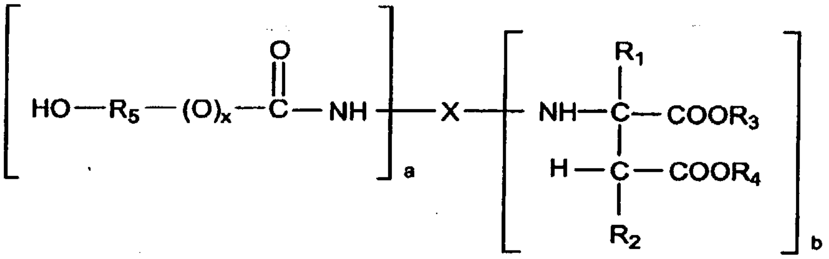
R_1 and R_2 may be identical or different and represent hydrogen or organic groups which are inert towards isocyanate groups at a temperatire of 100°C or less,

R_3 and R_4 may be identical or different and represent organic groups which are inert towards isocyanate groups at a temperatire of 100°C or less,

R_5 represents a member selected from the group consisting of C_2H_4, C_3H_6 and C_5H_{10}, a and b represent integers of from 1 to 5, provided that the sum of a and b is from 2 to 6 and

x is 1 when R_5 represents C_2H_4 or C_3H_6 and represents 0 when R_5 represents C_5H_{10}.

2. A process for preparing an asparatate of the formula:



$$\left[HO-R_5-(O)_x-\overset{\overset{O}{\|}}{C}-NH \right]_a X \left[\begin{array}{c} R_1 \\ | \\ NH-C-COOR_3 \\ | \\ H-C-COOR_4 \\ | \\ R_2 \end{array} \right]_b$$

where

X represents an m-valent organic residue obtained by removing the primary amino group or groups from a mono or polyamine which has (cyclo)aliphatically bound amino groups and a number average molecular weight of 60 to 6000, and which may contain further functional groups that either are reactive with isocyanate groups or are inert to isocyanate groups at temperatures of up to 100°C,

R_1 and R_2 may be identical or different and represent hydrogen or organic groups which are inert towards isocyanate groups at a temperatire of $100^{O}C$ or less (both are preferably hydrogen),

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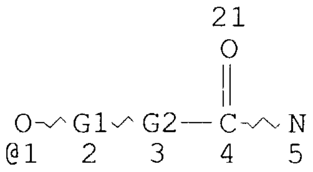

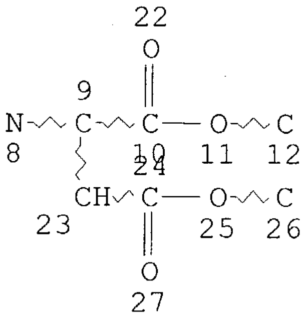

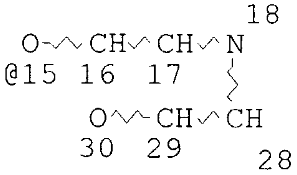

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
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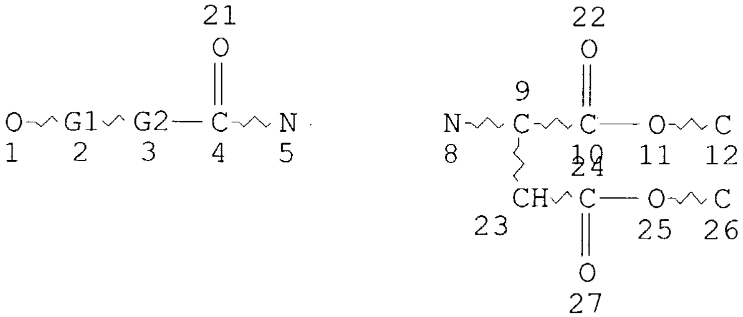

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REP G1=(2-5) C
REP G2=(0-1) O
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STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01


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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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L9   ANSWER 1 OF 10  ZCAPLUS  COPYRIGHT 2004 ACS on STN
2002:661461    Document No. 137:338122  Enantioselective Synthesis of the
     Protein Phosphatase Inhibitor (-)-Motuporin.  Hu, Tao; Panek, James
     S. (Department of Chemistry, Metcalf Center for Science and
     Engineering, Boston University, Boston, MA, 02215, USA).  Journal of
     the American Chemical Society, 124(38), 11368-11378 (English) 2002.
```

CODEN: JACSAT. ISSN: 0002-7863. Publisher: American Chemical Society.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

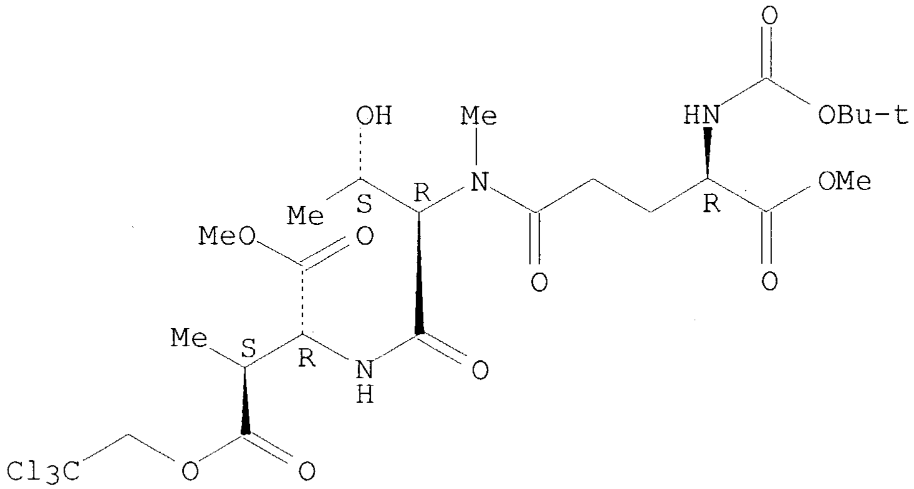
AB A highly convergent asym. synthesis of the protein phosphatase inhibitor motuporin is described. Synthesis and coupling of the individual peptide fragments followed by macrocyclization afforded the fully protected motuporin precursor I, which was converted to the natural product by dehydration and ester hydrolysis. Six of the eight stereogenic centers assocd. with the natural product were introduced using asym. crotylsilane bond construction methodol. The trisubstituted (E,E)-diene system of the motuporin side chain was obtained by a modified Negishi cross-coupling reaction: alkyne II was reacted with Schwartz' reagent [Cp2Zr(H)Cl] and ZnCl2 in THF to afford a vinyl zinc intermediate, which was then coupled with dipeptide iodoalkene III. Improved reaction conditions for macrocyclization are given.

IT **226067-09-0P 226067-32-9P**
(asym. synthesis of the protein phosphatase inhibitor motuporin)

RN 226067-09-0 ZCAPLUS

CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl-N-methyl-D-threonyl-3-methyl-, 1,31-dimethyl 34-(2,2,2-trichloroethyl) ester, (3S)- (9CI) (CA INDEX NAME)

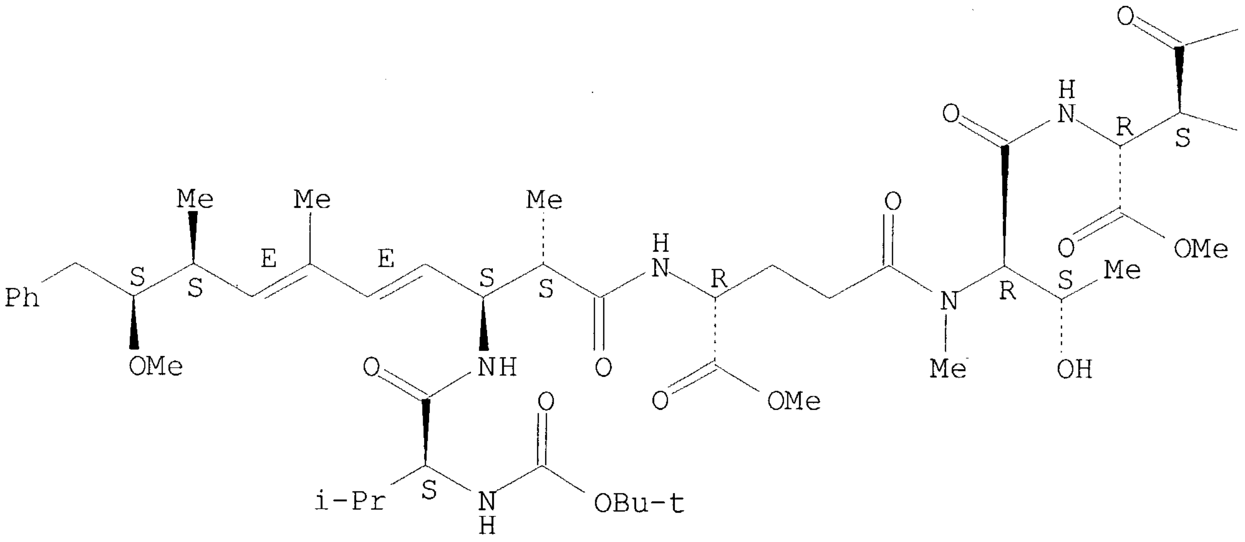
Absolute stereochemistry. Rotation (+).



RN 226067-32-9 ZCAPLUS
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-(2S,3S,4E,6E,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoyl-D-γ-glutamyl-N-methyl-D-threonyl-3-methyl-, 3,51-dimethyl 54-(2,2,2-trichloroethyl) ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



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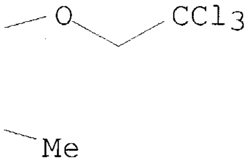
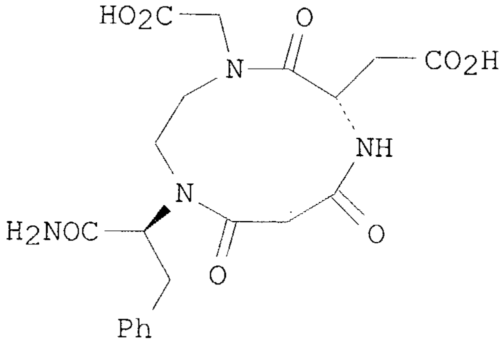


IT **226067-09-0P 226067-32-9P**
(asym. synthesis of the protein phosphatase inhibitor motuporin)

L9 ANSWER 2 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
2002:457919 Document No. 137:169783 Ni-to-Ni + 3-Ethylene-Bridged Partially Modified Retro-Inverso Tetrapeptide β-Turn Mimetic: Design, Synthesis, and Structural Characterization. Han, Yinglin; Giragossian, Craig; Mierke, Dale F.; Chorev, Michael (Department of Medicine, Bone and Mineral Metabolism Unit, Charles A. Dana and

Thorndike Laboratories, Beth Israel Deaconess Medical Center-Harvard Medical School, Boston, MA, 02215, USA). Journal of Organic Chemistry, 67(15), 5085-5097 (English) 2002. CODEN: JOCEAH. ISSN: 0022-3263. OTHER SOURCES: CASREACT 137:169783. Publisher: American Chemical Society.

GI



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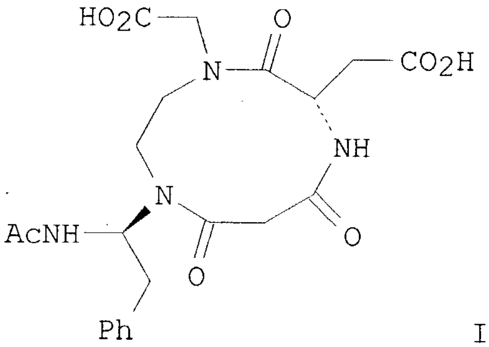

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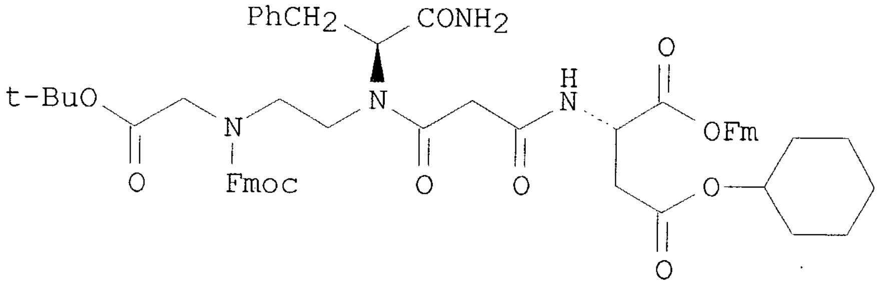


III

AB Cyclic peptidomimetics I and II, 1,3,8-trisubstituted 2,5,7-trioxo-1,4,8-triazadecane that represents a Ni-to-Ni+3-ethylene-bridged partially modified retro-inverso β-turn, were synthesized and structurally analyzed. These compds. utilize an ethylene bridge to replace the COi···HNi+3 10-membered hydrogen bond of std. β-turns. Synthesis of I and II involved, first, the prepn. of the intermediate N,N'-ethylene-bridged dimer (S)-t-BuO2CCH2N(Fmoc)CH2CH2NHCH(CH2Ph)CONH2via reductive alkylation of H-Phe-NH2 with FmocN(CH2CHO)CH2CO2Bu-t. An orthogonal protection strategy and HATU-mediated couplings allowed efficient stepwise addns. of monomeric building blocks leading to a Ni-to-Ni+3-ethylene-bridged linear peptidomimetic III (OFm = 9-fluorenylmethoxy). Further elaboration of the III generated I and II (H2N-rPheN-mGly-Asp-NGly-OH and Ac-gPheN-mGly-Asp-NGly-OH, resp.;

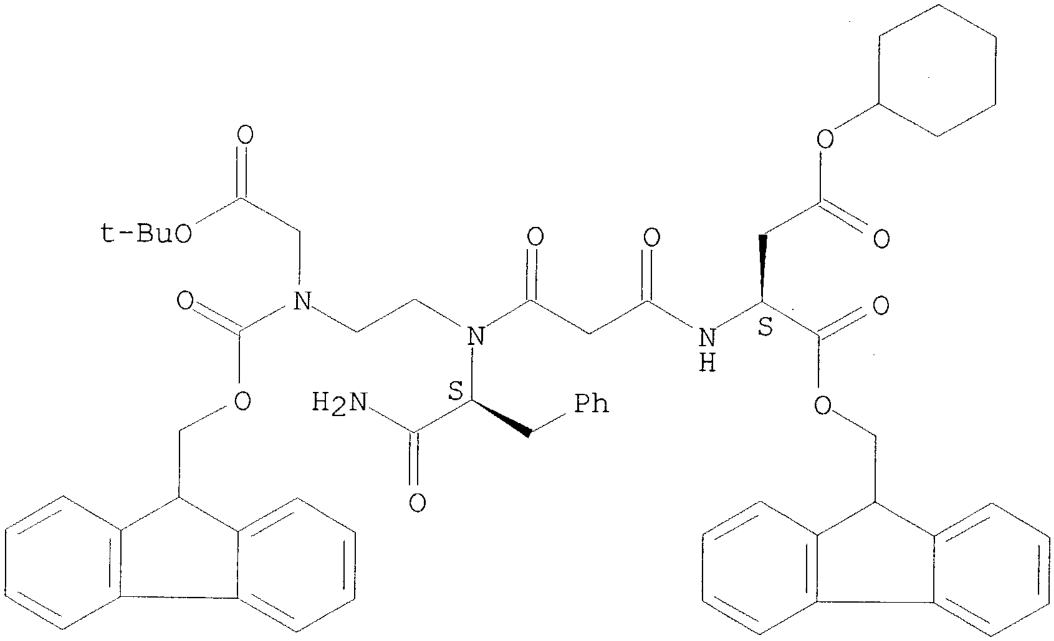
g = gem-diaminoalkyl, m = malonyl, r = direction-reversed amino acid) in 44 and 39% yields, resp. The structural features of I and II were detd. using 1H NMR and extensive computer simulations. The results indicated that the 10-membered rings are conformationally constrained with well-defined structural features and that the three amide bonds in the ring are in the trans orientation. The topol. arrangement of the residues in the ring system closely resembles a type II' β-turn. Transformation of CONH2 in the N-terminal amino acid residue of I into NHCOCH3 in II resulted in the formation of a hydrogen bond between the NH of gPhe-COCH3 and the C-terminal carboxyl of Gly, initiating an antiparallel β-sheet.

IT **446880-43-9P**
(prepn. and structure anal. of ethylene-bridged, retro-inverso, cyclic tetrapeptides as β-turn mimetics)

RN 446880-43-9 ZCAPLUS

CN L-Aspartic acid, N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-N-[2-[[2-(1,1-dimethylethoxy)-2-oxoethyl][(9H-fluoren-9-ylmethoxy)carbonyl]amino]ethyl]-3-oxo-β-alanyl-, 24-cyclohexyl 21-(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **446880-43-9P**
(prepn. and structure anal. of ethylene-bridged, retro-inverso, cyclic tetrapeptides as β-turn mimetics)

L9 ANSWER 3 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN

2001:499015 Document No. 135:318682 Design and preparation of serine-threonine protein phosphatase inhibitors based upon the nodularin and microcystin toxin structures. Part 3. Webster, Kerri L.; Maude, Antony B.; O'Donnell, Michael E.; Mehrotra, Amit P.; Gani, David (School of Chemistry and Centre for Biomolecular Sciences, The University, St. Andrews, Fife, KY16 9ST, UK). Journal of the Chemical Society, Perkin Transactions 1 (14), 1673-1695 (English) 2001. CODEN: JCSPCE. ISSN: 1472-7781. OTHER SOURCES: CASREACT 135:318682. Publisher: Royal Society of Chemistry.

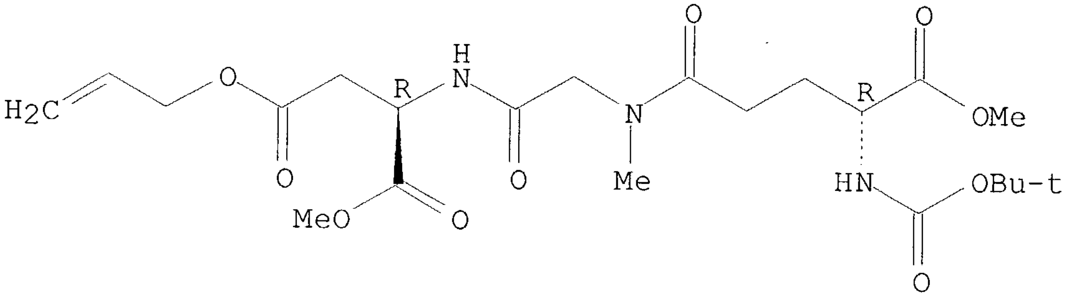
AB Nodularin and microcystins are complex natural cyclic isopeptidic hepatotoxins that serve as subnanomolar inhibitors of the eukaryotic serine-threonine protein phosphatases PP1 and PP2A, enzymes that are intimately involved in controlling cellular metab. Previously we described a soln.-phase synthesis of stripped-down nodularin analogs; cyclo[-β-Ala-(R)-Glu-α-OMe-γ-Sar-(R)-Asp-α-OMe-β-(S)-Phe-] (I) and cyclo[-(3R)-3-hydroxymethyl-β-Ala-(R)-Glu-α-OMe-γ-Sar-(R)-Asp-α-OMe-β-(S)-Phe-] (II). The synthetic strategy was designed to allow post-macrocyclization elaboration. Here we examine alternative methods for introducing diversity and achieving macrolactamization and compare the relative efficiency of soln.- vs. solid-phase peptide syntheses of the macrocycles. Syntheses and the biol. activities of the macrocycles cyclo-[(2R)-α-4-benzylpiperidinylamido-Asp]-β-[(R)-Glu]-γ-Sar-[(R)-Asp]-β-(S)-Phe- (III) and cyclo-(2S)-Phe-[(2R)-α-4-benzylpiperidinylamido-Asp]-(R)-Glu-γ-(S)-Pro-β-(R)-Asp-(IV) are compared. Both compds. contain sufficient side-chain functionality to interact with a hydrophobic groove at the enzyme active site. The proline contg. analogs where sarcosine is replaced in macrocycles I and 4, were also synthesized in order to correlate conformational properties with biol. activity. In accord with predictions macrocycles III and IV were found to be weak inhibitors of PP1 with IC50 2.9 and 2.7 mM resp.

IT **368443-52-1P 368443-53-2P 368443-58-7P**
368443-60-1P
(prepn. of serine-threonine protein phosphatase inhibitors based upon the nodularin and microcystin toxin structures)

RN 368443-52-1 ZCAPLUS

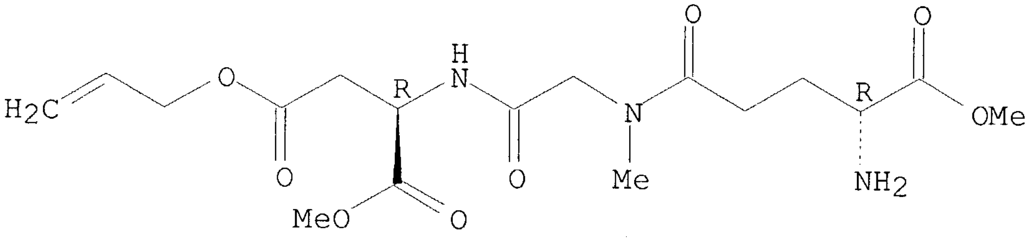
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl-N-methylglycyl-, 1,31-dimethyl 34-(2-propenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 368443-53-2 ZCAPLUS
CN D-Aspartic acid, D-γ-glutamyl-N-methylglycyl-, 1,31-dimethyl 34-(2-propenyl) ester, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

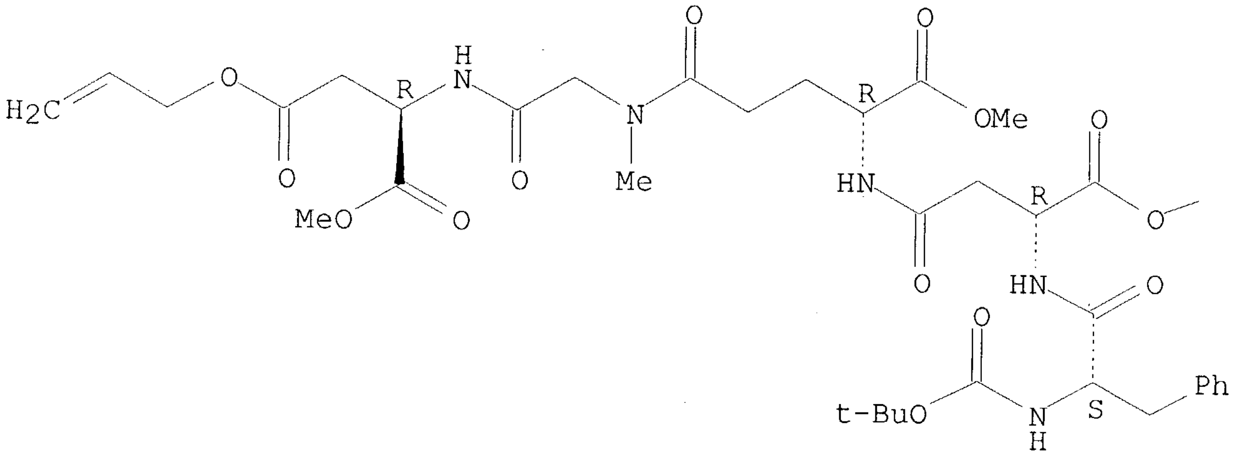


● HCl

RN 368443-58-7 ZCAPLUS
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-D-β-aspartyl-D-γ-glutamyl-N-methylglycyl-, 51-methyl 2-(phenylmethyl) 54-(2-propenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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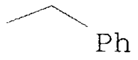
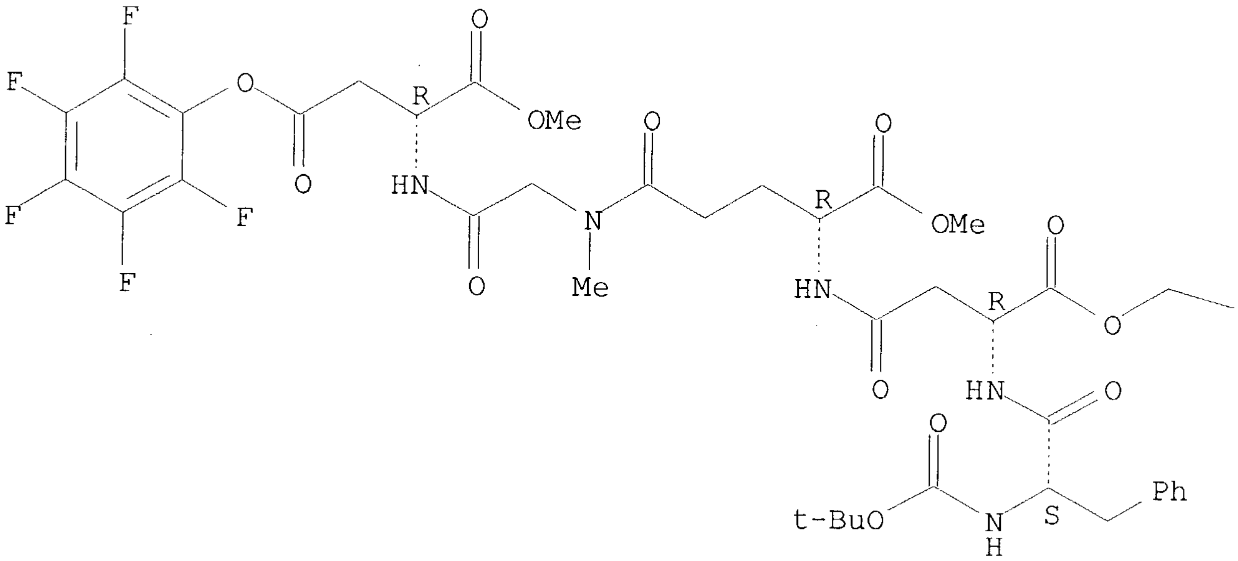


RN 368443-60-1 ZCAPLUS

CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-D-β-aspartyl-D-γ-glutamyl-N-methylglycyl-, 51-methyl 54-(pentafluorophenyl) 2-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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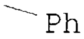


IT **368443-52-1P 368443-53-2P 368443-58-7P**
368443-60-1P
(prepn. of serine-threonine protein phosphatase inhibitors based upon the nodularin and microcystin toxin structures)

L9 ANSWER 4 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
2000:894596 Document No. 134:237788 Partially-modified retro-inverso β-turn tetrapeptidomimetic. Han, Yinglin; Chorev, Michael (Division of Bone & Mineral Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA). Peptides for the New Millennium, Proceedings of the American Peptide

Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999, Meeting Date 1999, 157-158. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth. (English) 2000. CODEN: 69ATHX.

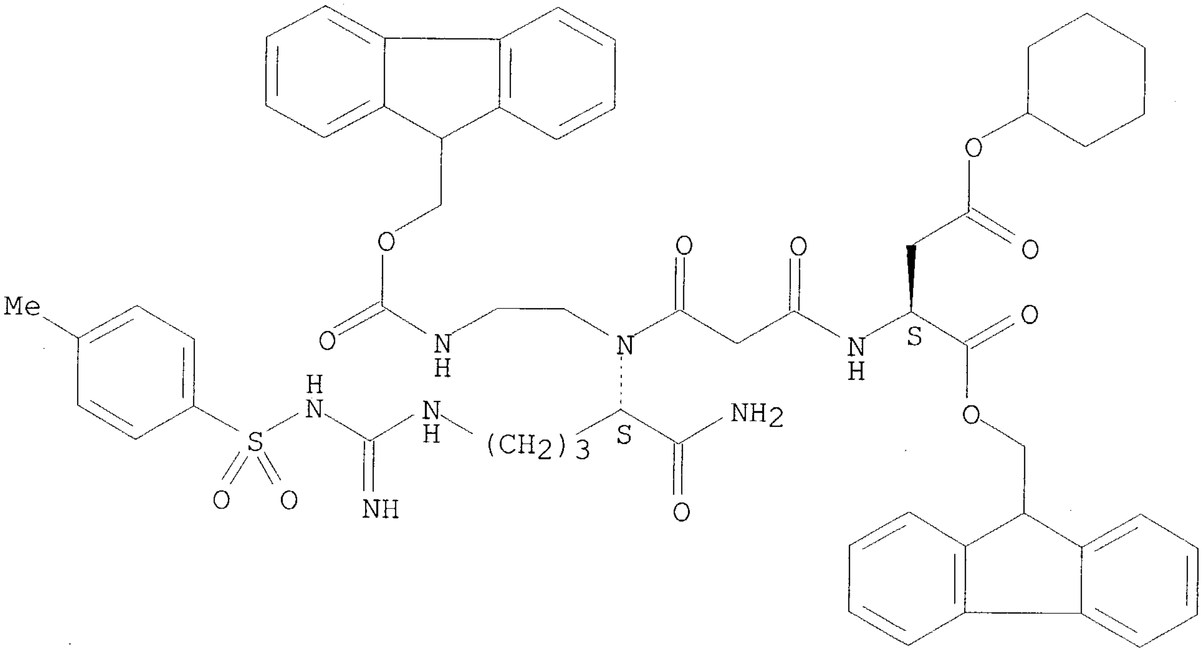
AB A symposium on the authors' work in synthesizing the ten-membered title compds.

IT **330187-50-3P**
(prepn. of modified retro-inverso β-turn tetrapeptidomimetic compds.)

RN 330187-50-3 ZCAPLUS

CN L-Aspartic acid, N-[(1S)-1-(aminocarbonyl)-4-[[imino[[(4-methylphenyl)sulfonyl]amino]methyl]amino]butyl]-N-[2-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]ethyl]-3-oxo-β-alanyl-, 24-cyclohexyl 21-(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



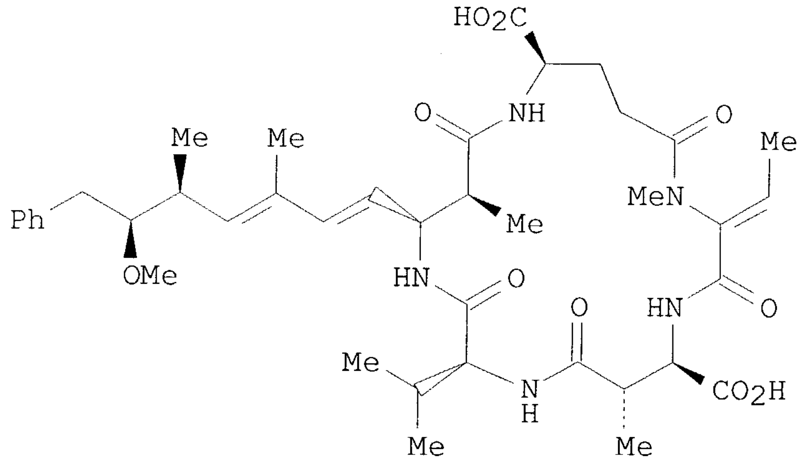
IT **330187-50-3P**
(prepn. of modified retro-inverso β-turn tetrapeptidomimetic compds.)

L9 ANSWER 5 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN

1999:234571 Document No. 131:19273 Total synthesis of (-)-Motuporin. Hu, Tao; Panek, James S. (Department of Chemistry Metcalf Center for Science and Engineering, Boston University, Boston, MA, 02215, USA). Journal of Organic Chemistry, 64(9), 3000-3001 (English) 1999.

CODEN: JOCEAH. ISSN: 0022-3263. Publisher: American Chemical Society.

GI



I

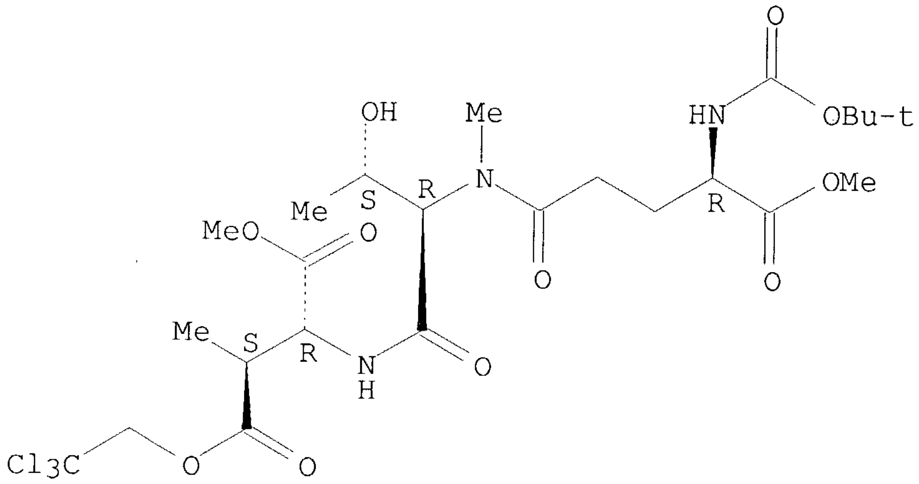
AB This communication reports a highly convergent, asym. synthesis of (-)-motuporin (I). The synthesis utilized an efficient Pd(0)-catalyzed cross-coupling reaction of a configurationally well-defined vinyl zinc intermediate with an (E)-vinyl iodide for the construction of the trisubstituted (E,E)-diene in a peptidic system. Six of the eight stereogenic centers assocd. with I were introduced using asym. crotylsilane bond construction methodol.

IT **226067-09-0P 226067-32-9P**
(total synthesis of (-)-motuporin)

RN 226067-09-0 ZCAPLUS

CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl-N-methyl-D-threonyl-3-methyl-, 1,31-dimethyl 34-(2,2,2-trichloroethyl) ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

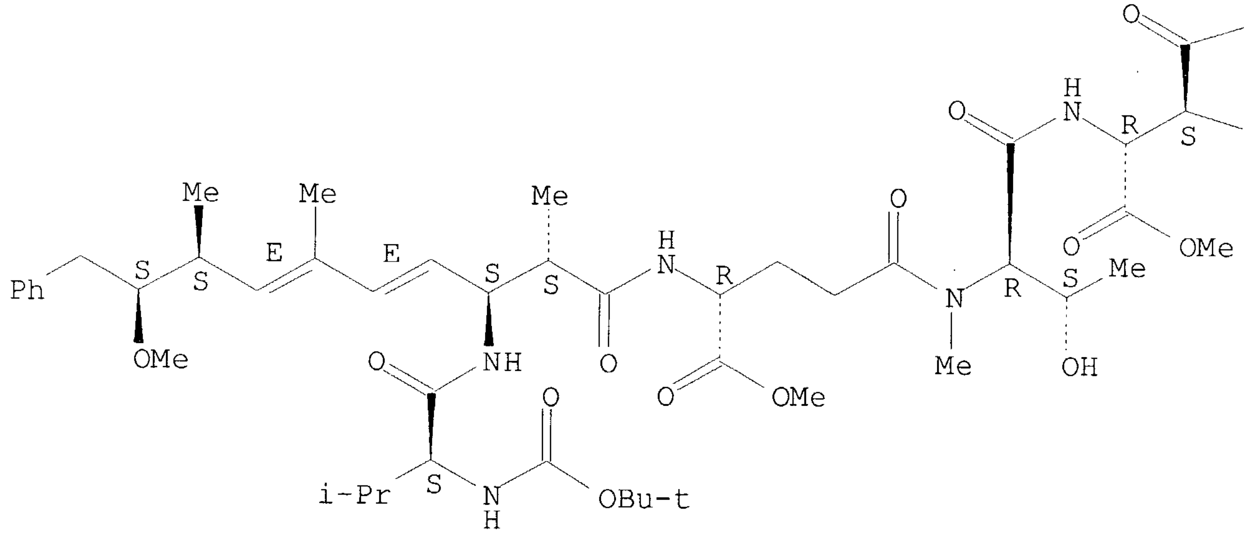


RN 226067-32-9 ZCAPLUS

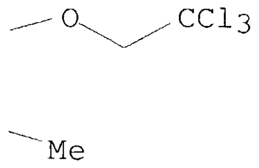
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-(2S,3S,4E,6E,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoyl-D-γ-glutamyl-N-methyl-D-threonyl-3-methyl-, 3,51-dimethyl 54-(2,2,2-trichloroethyl) ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



IT 226067-09-0P 226067-32-9P
(total synthesis of (-)-motuporin)

L9 ANSWER 6 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
1997:628653 Document No. 127:293610 Design and preparation of serine-threonine protein phosphatase inhibitors based upon the nodularin and microcystin toxin structures: Part 2. Synthesis of a functionalized nodularin macrocycle and a stripped-down microcystin macrocycle. Maude, Antony B.; Mehrotra, Amit P.; Gani, David (School of Chemistry and Centre for Biomolecular Sciences, The University, St. Andrews, KY16 9ST, UK). Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (17), 2513-2526 (English) 1997. CODEN: JCPRB4. ISSN: 0300-922X. Publisher: Royal Society of Chemistry.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Nodularins and microcystins are complex natural isopeptidic hepatotoxins that serve as subnanomolar inhibitors of the eukaryotic serine-threonine protein phosphatases, PP1 and PP2A. Previously (A. P. Mehrotra, et. al, 1997), each of the key structural or potentially reactive motifs within each macrocycle type was assessed as a contributor towards phosphatase inhibitory efficacy and a stripped-down nodularin-type macrocycle was identified as a suitable precursor to potentially active synthetic inhibitors. Subsequently, synthetic routes to the 19-membered nodularin macrocyclic system were developed, using soln.-phase chem., which demonstrated that only certain cyclization protocols were viable. Here the authors describe an extension of this chem. to provide 19-membered nodularin macrocycle I appropriately functionalized with a hydroxymethyl group for the incorporation of lipophilic side-chains. The authors also demonstrated that 25-membered microcystin macrocycle II can be prepd. in good yield using similar protocols in which macrocyclization is effected through the reaction of the amino group of the L-Phe residue with the β-pentafluorophenyl ester of the

D-Asp residue.

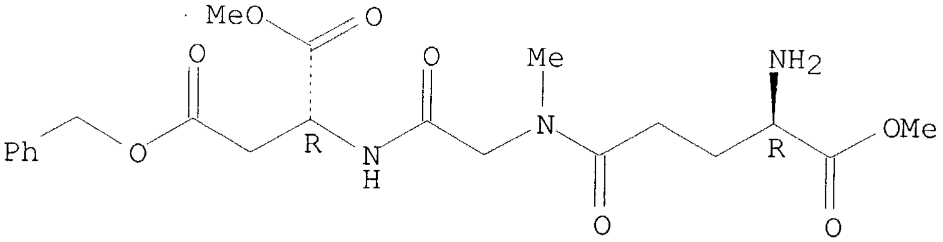
IT **196938-92-8**

(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

RN 196938-92-8 ZCAPLUS

CN D-Aspartic acid, D-γ-glutamyl-N-methylglycyl-, 1,31-dimethyl 34-(phenylmethyl) ester, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

IT **182748-81-8P 182748-82-9P 196950-39-7P**
196950-44-4P

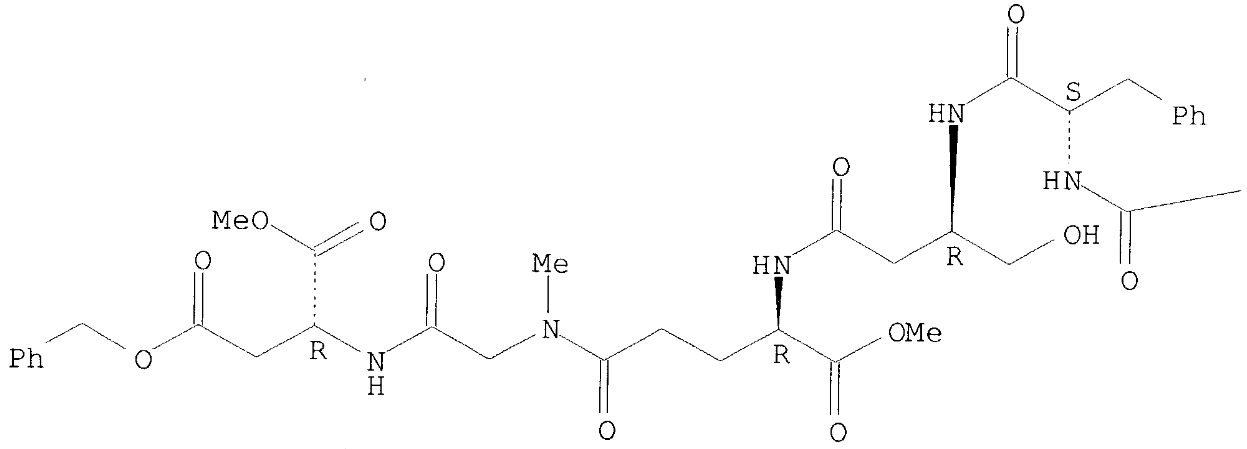
(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

RN 182748-81-8 ZCAPLUS

CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-4-hydroxy-(R)-3-aminobutanoyl-D-γ-glutamyl-N-methylglycyl-, 3,51-dimethyl 54-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



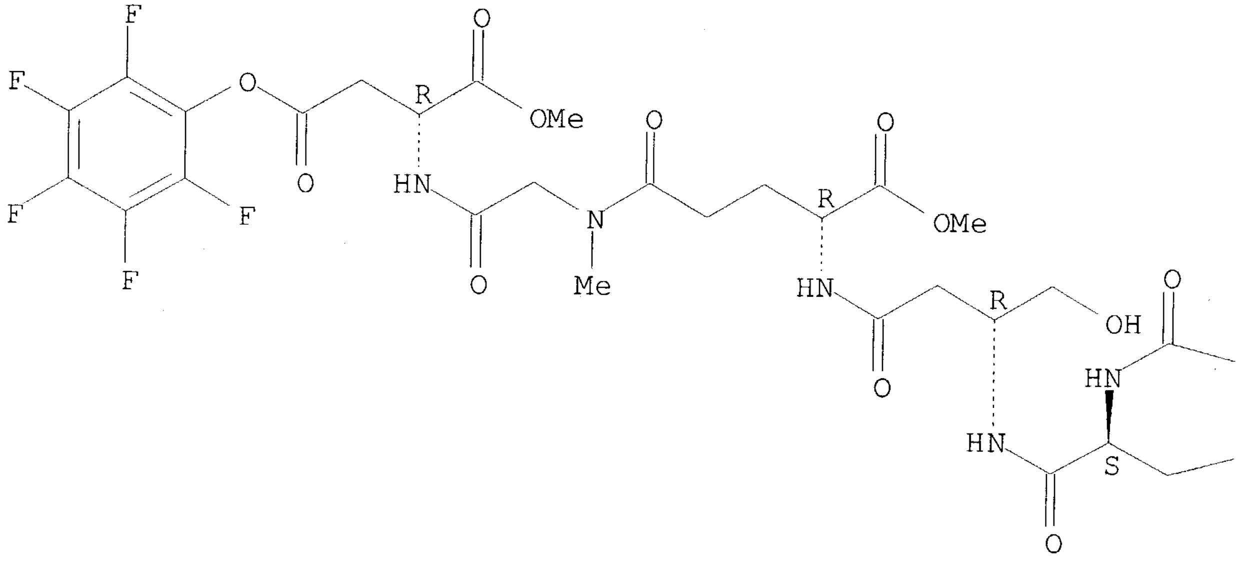
PAGE 1-B

RN 182748-82-9 ZCAPLUS

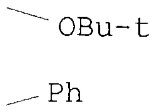
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-4-hydroxy-(R)-3-aminobutanoyl-D-γ-glutamyl-N-methylglycyl-, 3,51-dimethyl 54-(pentafluorophenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



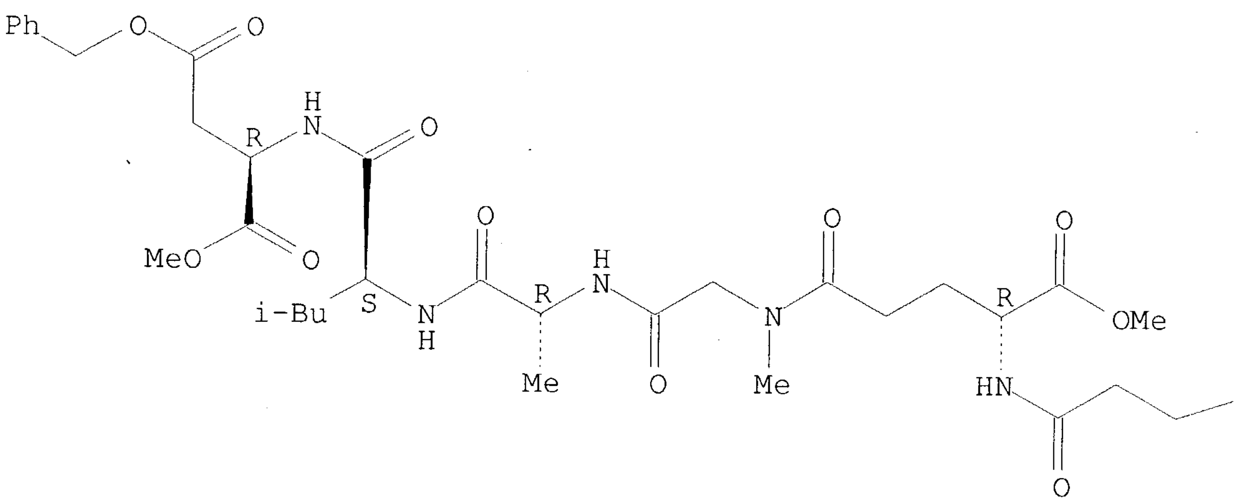
PAGE 1-B



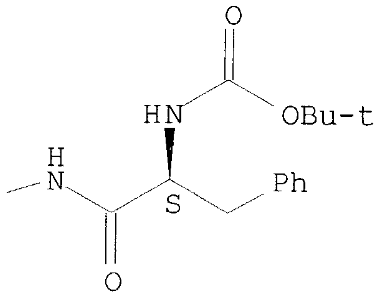
RN 196950-39-7 ZCAPLUS
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-
β-alanyl-D-γ-glutamyl-N-methylglycyl-D-alanyl-L-leucyl-,
3,71-dimethyl 74-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



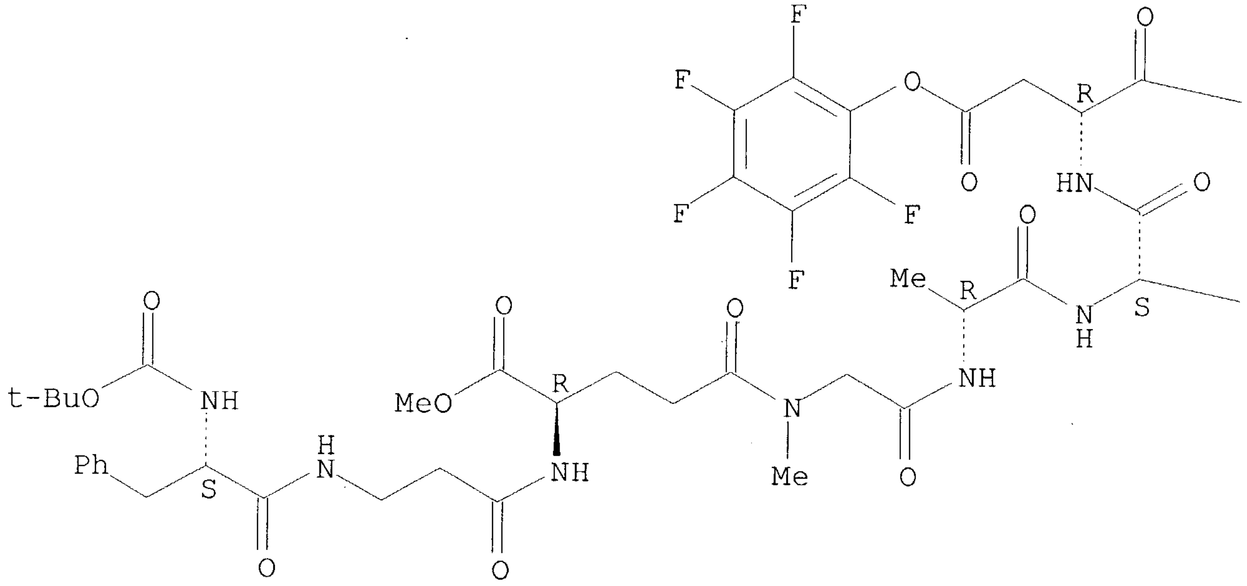
PAGE 1-B



RN 196950-44-4 ZCAPLUS
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-β-alanyl-D-γ-glutamyl-N-methylglycyl-D-alanyl-L-leucyl-, 3,71-dimethyl 74-(pentafluorophenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

IT **196938-92-8**

(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

IT **182748-81-8P 182748-82-9P 196950-39-7P**
196950-44-4P

(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

L9 ANSWER 7 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
1997:628652 Document No. 127:293609 Design and preparation of serine-threonine protein phosphatase-inhibitors based upon the nodularin and microcystin toxin structures. Part 1. Evaluation of key inhibitory features and synthesis of a rationally stripped-down nodularin macrocycle. Mehrotra, Amit P.; Webster, Kerri L.; Gani, David (School of Chemistry and Centre for Biomolecular Sciences, The University, St. Andrews, KY16 9ST, UK). Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (17), 2495-2511 (English) 1997. CODEN: JCPRB4. ISSN: 0300-922X. Publisher: Royal Society of Chemistry.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The natural nodularin and microcystin toxins are powerful but non-selective inhibitors of the ubiquitous and structurally related eukaryotic Ser-Thr protein phosphatases, PP1 and PP2A, enzymes that are intimately involved in controlling cellular metab. Both families of toxin are cyclic tri-isopeptides typified by the presence of two free carboxylic acid groups, a dehydroamino acid moiety, and a large, rigid exocyclic lipophilic side-chain. To learn how to design specific inhibitors for each enzyme, the nature of specific interactions with potential inhibitor-conferring moieties in the toxin was considered. Borohydride redn. of the dehydroalanine residue present in microcystin-LR (I), a potential Michael acceptor, gave two diastereoisomeric dihydromicrocystin products. Each of these displayed subnanomolar activities as inhibitors for PP2A, as for the parent compd., indicating that the dehydroamino acid residue in microcystin and, probably, in nodularin, is not essential for activity. Other conserved features appeared to be required to confer activity, hence strategies towards the synthesis of simplified non-dehydroamino acid-contg. analogs of each macrocycle type were considered. In each case it was planned to elaborate the lipophilic side-chain functionality after the formation of the macrocyclic ring. In order to synthesize the precursor nodularin-type macrolactam, two peptide-bond disconnections of the ring were investigated using model system II, one bond disconnecting between the Sar carboxy group and the D-Asp N-atom (disconnection A), and the other disconnecting between the D-Asp β-carboxy group and the L-Phe N-atom (disconnection B). Prepn. of the linear precursors was achieved using soln.-phase chem. without incident. Macrolactamization via the displacement of the β-pentafluorophenyl ester of the D-Asp α-Me ester residue by the free amino group of the L-Phe residue proceeded in excellent yield (89%), but the alternative strategy failed. Application of the successful macrolactamization strategy to other nodularin macrocycles and to the construction of the microcystin-type macrocycle is described in the following article.

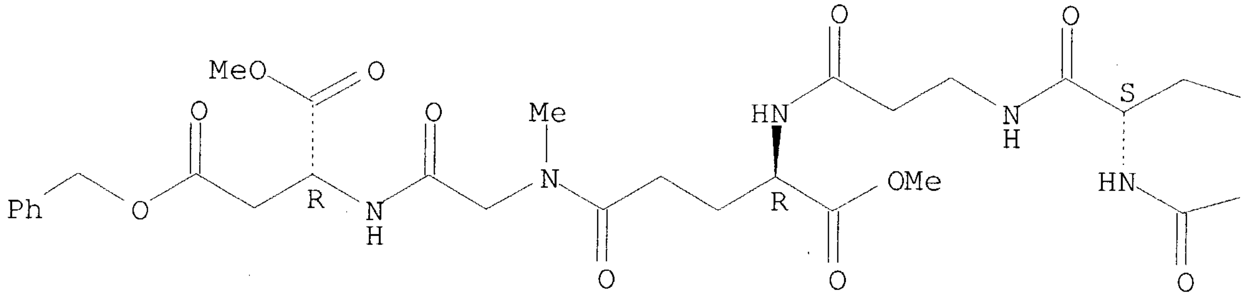
IT **182748-71-6P 182748-75-0P 182748-80-7P**
196938-92-8P
(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

RN 182748-71-6 ZCAPLUS

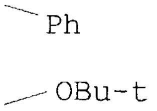
CN D-Aspartic acid, N-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



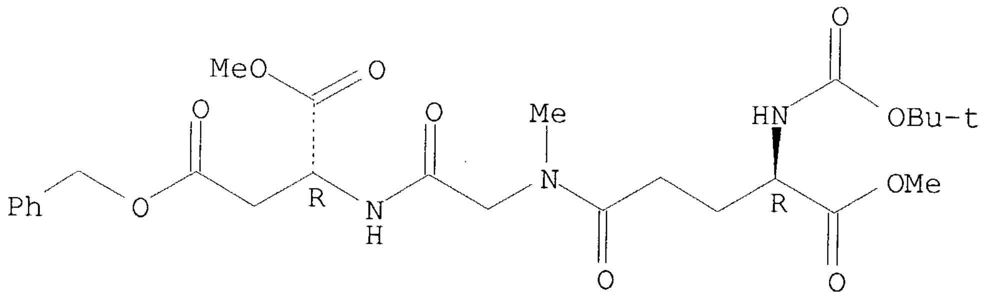
PAGE 1-B



RN 182748-75-0 ZCAPLUS

CN D-Aspartic acid, N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(phenylmethyl) ester (9CI) (CA INDEX NAME)

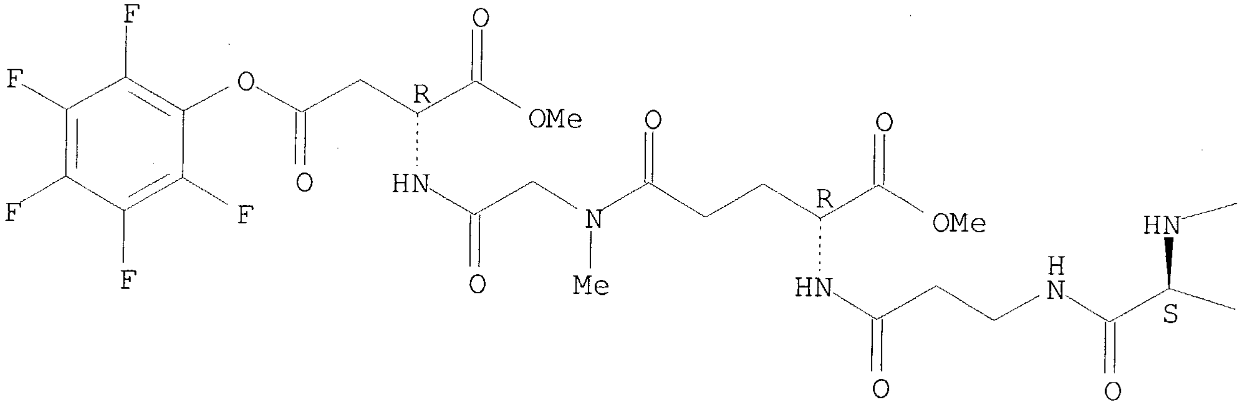
Absolute stereochemistry.



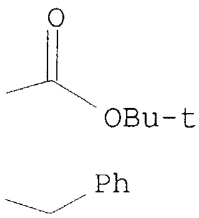
RN 182748-80-7 ZCAPLUS
CN D-Aspartic acid, N-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(pentafluorophenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

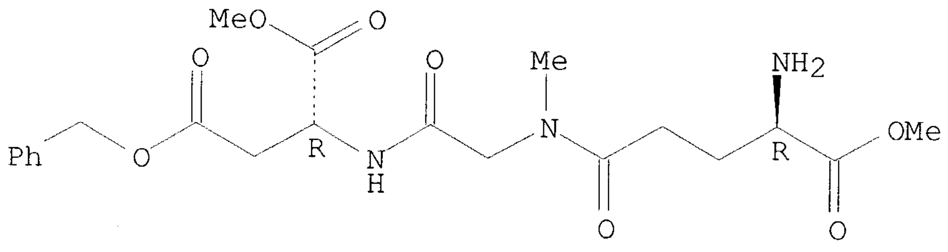


PAGE 1-B



RN 196938-92-8 ZCAPLUS
CN D-Aspartic acid, D-γ-glutamyl-N-methylglycyl-, 1,31-dimethyl
34-(phenylmethyl) ester, monohydrochloride (9CI) (CA INDEX NAME)

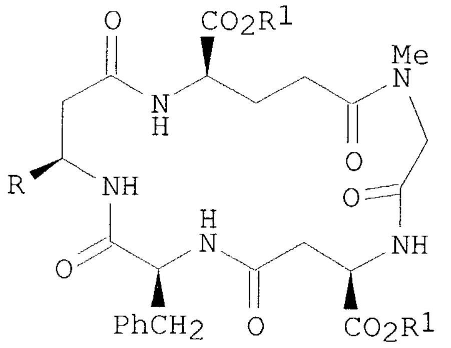
Absolute stereochemistry.



● HCl

IT **182748-71-6P 182748-75-0P 182748-80-7P**
196938-92-8P
(design and prepn. of serine-threonine protein phosphatase-inhibitors based on nodularin and microcystin toxin structures)

L9 ANSWER 8 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
1996:585143 Document No. 125:301552 Synthesis of functionalized cyclic pentapeptide analogs of the serine-threonine protein phosphatase inhibitor nodularin. Mehrotra, Amit P.; Gani, David (School of Chem. and Centre of Biomolecular Sci., Univ. of St. Andrews, Fife, KY16 9ST, UK). Tetrahedron Letters, 37(38), 6915-6918 (English) 1996. CODEN: TELEAY. ISSN: 0040-4039. Publisher: Elsevier.
GI



I

AB A generic synthesis of nodularin cyclopeptide analogs I (R = H, CH2OH; R1 = Me, Li) incorporating suitable functionality for synthetic elaboration is described, providing access to new protein phosphatase inhibitors.

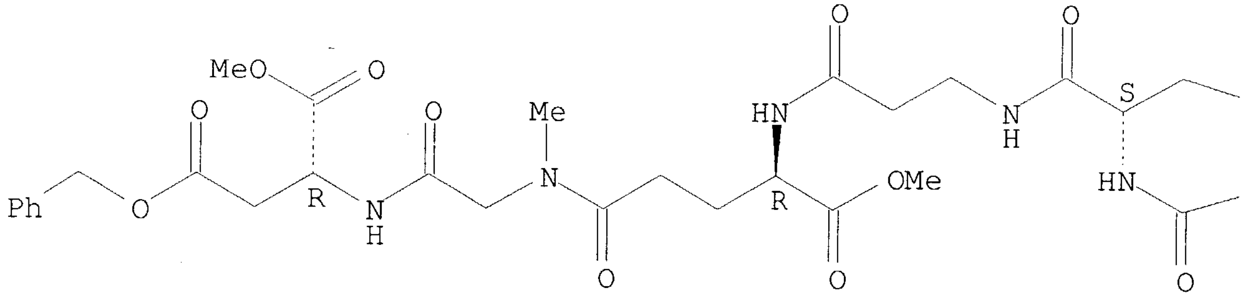
IT **182748-71-6P 182748-75-0P 182748-80-7P**
182748-81-8P 182748-82-9P
(prepn. of functionalized nodularin cyclopeptide analogs)

RN 182748-71-6 ZCAPLUS

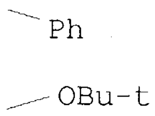
CN D-Aspartic acid, N-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



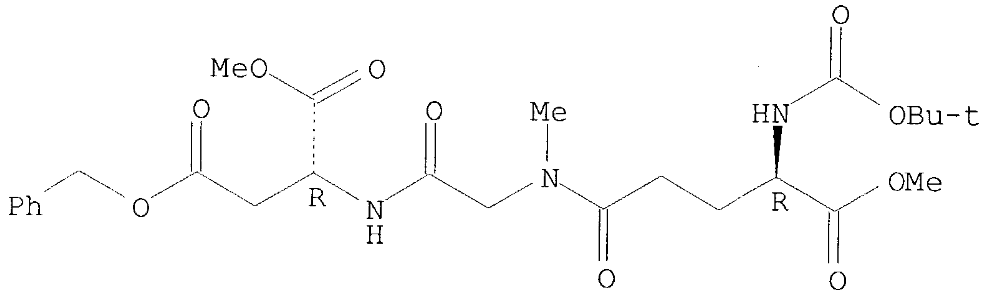
PAGE 1-B



RN 182748-75-0 ZCAPLUS

CN D-Aspartic acid, N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(phenylmethyl) ester (9CI) (CA INDEX NAME)

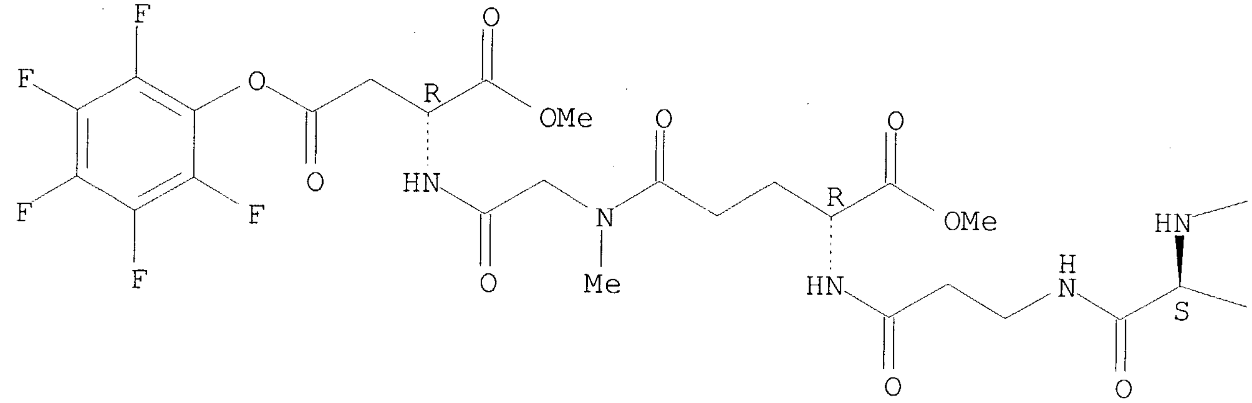
Absolute stereochemistry.



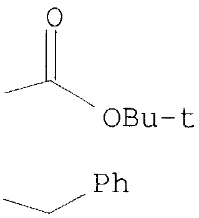
RN 182748-80-7 ZCAPLUS
CN D-Aspartic acid, N-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]-D-γ-glutamyl]-N-methylglycyl]-, 1,1'-dimethyl 4-(pentafluorophenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

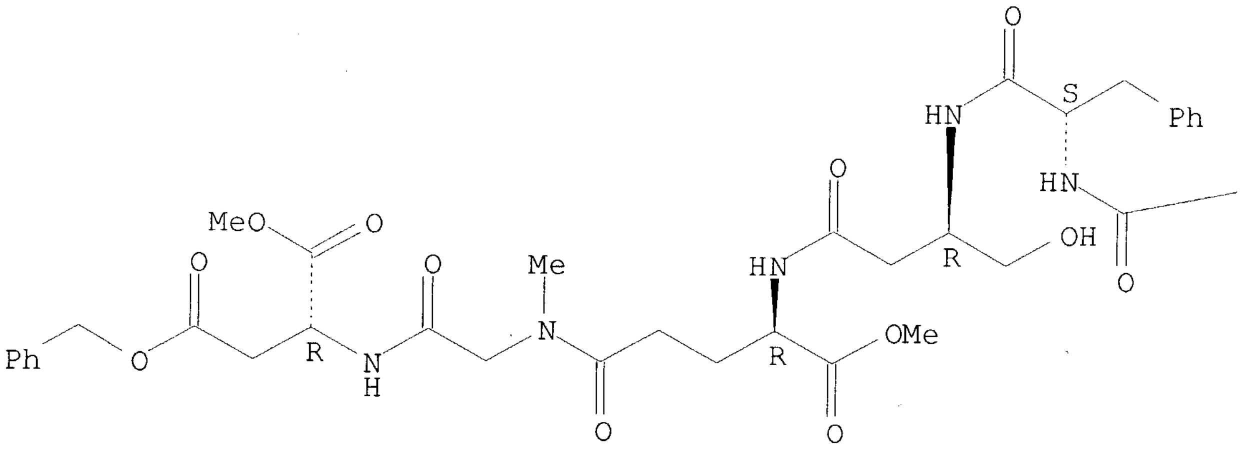


RN 182748-81-8 ZCAPLUS

CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-4-hydroxy-(R)-3-aminobutanoyl-D-γ-glutamyl-N-methylglycyl-, 3,51-dimethyl 54-(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



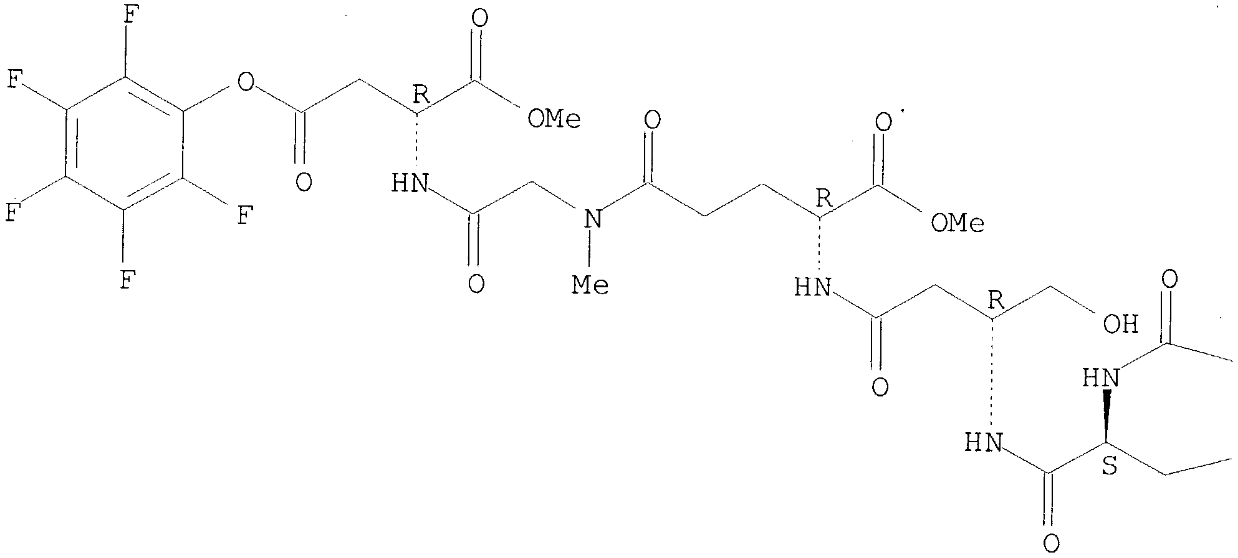
PAGE 1-B

RN 182748-82-9 ZCAPLUS

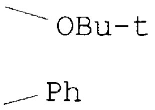
CN D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-4-hydroxy-(R)-3-aminobutanoyl-D-γ-glutamyl-N-methylglycyl-, 3,51-dimethyl 54-(pentafluorophenyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT **182748-71-6P 182748-75-0P 182748-80-7P**
182748-81-8P 182748-82-9P
(prepn. of functionalized nodularin cyclopeptide analogs)

L9 ANSWER 9 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
1995:751084 Document No. 124:30333 Enantiospecific total synthesis of the protein phosphatase inhibitor motuporin.. Valentekovich, Robert

J.; Schreiber, Stuart L. (Department of Chemistry, Harvard University, Cambridge, MA, 02138, USA). Journal of the American Chemical Society, 117(35), 9069-70 (English) 1995. CODEN: JACSAT. ISSN: 0002-7863. OTHER SOURCES: CASREACT 124:30333. Publisher: American Chemical Society.

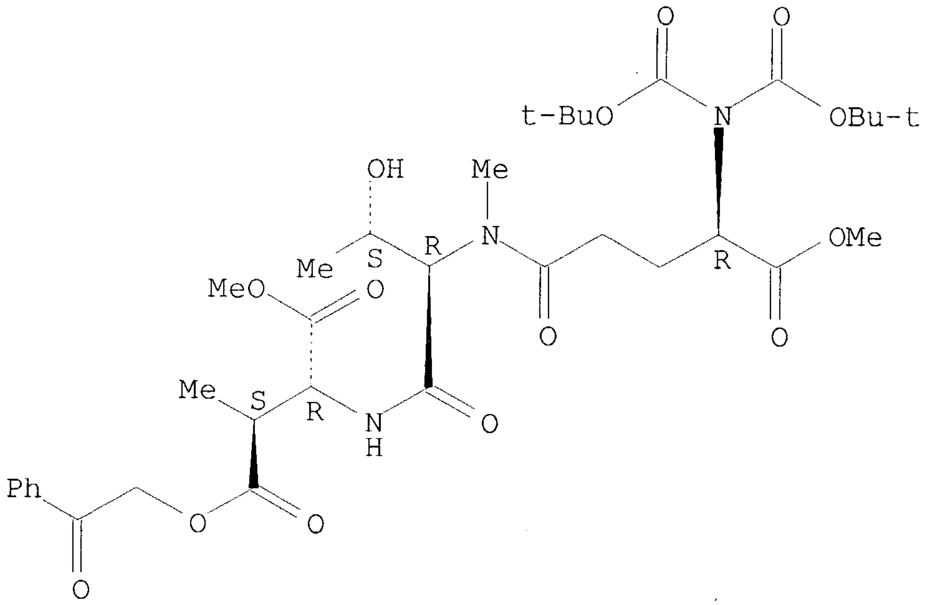
AB Motuporin (I) was prepd. by a convergent synthesis in which all stereocenters are derived from common amino acids or from D-mandelic acid; the 3 unusual amino acids in I are all derived from D-threonine.

IT **170872-83-0P 170872-84-1P**
(enantiospecific total synthesis of the protein phosphatase inhibitor motuporin)

RN 170872-83-0 ZCAPLUS

CN D-Aspartic acid, N-[N-[N,N-bis[(1,1-dimethylethoxy)carbonyl]-D-γ-glutamyl]-N-methyl-D-threonyl]-3-methyl-, 1,1'-dimethyl 4-(2-oxo-2-phenylethyl) ester, erythro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

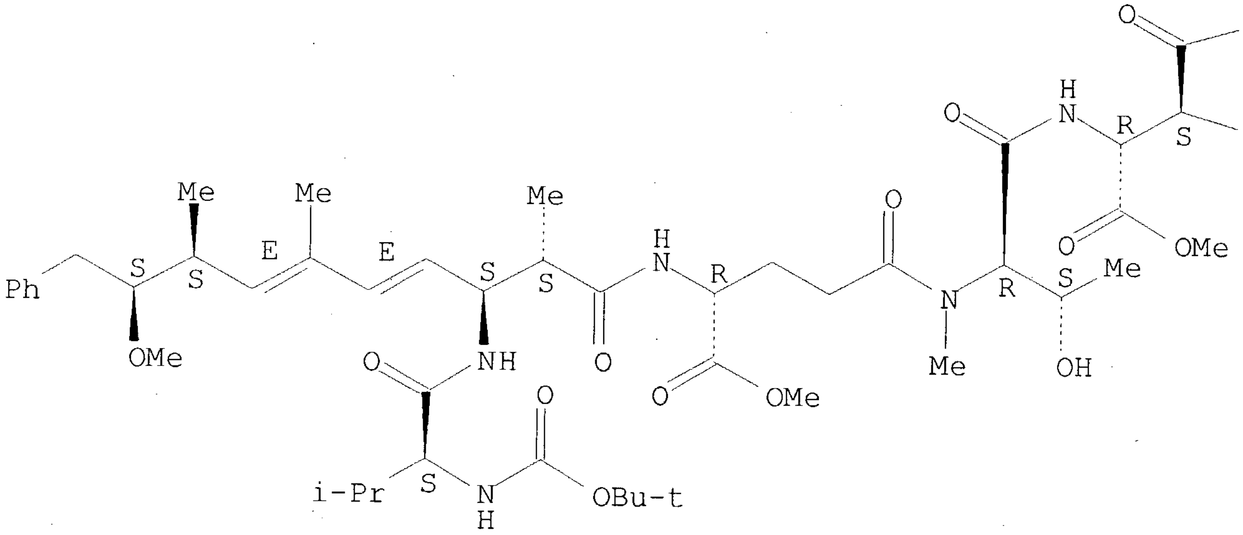


RN 170872-84-1 ZCAPLUS

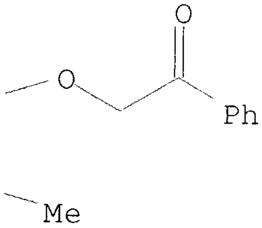
CN L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-(2S,3S,4E,6E,8S,9S)-4,5,6,7-tetradehydro-9-methoxy-2,6,8-trimethyl-10-phenyl-3-aminodecanoyl-D-γ-glutamyl-N-methyl-D-threonyl-3-methyl-, 1,1'-dimethyl 4-(2-oxo-2-phenylethyl) ester, erythro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



IT **170872-83-0P 170872-84-1P**
(enantiospecific total synthesis of the protein phosphatase inhibitor motuporin)

L9 ANSWER 10 OF 10 ZCAPLUS COPYRIGHT 2004 ACS on STN
1978:105744 Document No. 88:105744 Peptide sequencing: the utility of chemical ionization mass spectrometry. Mudgett, M.; Bowen, D. V.; Field, F. H.; Kindt, T. J. (Rockefeller Univ., New York, NY, USA). Biomedical Mass Spectrometry, 4(3), 159-71 (English) 1977. CODEN: BMSYAL. ISSN: 0306-042X.

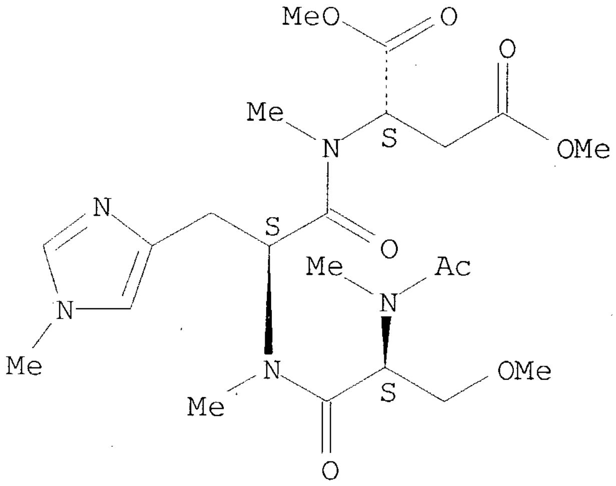
AB The sequences of permethylated acetyl peptides were detd. using low resoln. chem. ionization mass spectrometry. The method was tested using 45 peptides contg. 2-5 residues and all common amino acids except cysteine and N-terminal asparagine. Isobutane chem. ionization spectra contain 3 principal types of N-terminal sequence ion and one type of C-terminal ion; the redundant information from these 4 ions increases the reliablity of the detn.

IT **65564-46-7**
(chem. ionization mass spectrum of)

RN 65564-46-7 ZCAPLUS

CN L-Aspartic acid, N-[N-(N-acetyl-N,O-dimethyl-L-seryl)-N,1-dimethyl-L-histidyl]-N-methyl-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **65564-46-7**
(chem. ionization mass spectrum of)